Response to Office Action Mailed May 13, 2009

A. Claims In The Case

Claims 48, 81-93 and 95 have been rejected. Claim 48 has been amended. Claims 94, 96, and 97 have been withdrawn. Claims 48, 81-93, and 95 are pending in the case.

B. The Claims Are Not Obvious Over The Cited Art Pursuant To 35 U.S.C. § 103(a)

The Examiner has rejected claims 48 and 92 as being unpatentable over Gaudreau.

In order to reject a claim as obvious, the Examiner has the burden of establishing a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 USPQ 173, 177-178 (CCPA 1967). To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974), MPEP § 2143.03.

Claim 48 states:

A pharmaceutical composition, comprising:

a) a growth hormone-releasing hormone (GHRH) analogue or a pharmaceutically acceptable salt thereof in an amount effective to stimulate secretion or synthesis of growth hormone in a human in need thereof, said GHRH analogue or salt consisting of the formula: Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser-D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2; and

b) a pharmaceutically acceptable carrier.

The Office Action concedes that Gaudreau does not teach a pharmaceutical composition comprising the claimed GHRH analog. The Office Action, however, alleges that:

> "it would have been obvious to make this GHRH analogue and to dissolve it in a pharmaceutically-acceptable carrier at a concentration effective to stimulate secretion or synthesis of growth hormone. The skilled artisan would have been motivated to do so based on the teaching of Gaudreau that the GNRH analogue above possess biological activity, a binding affinity to the receptor in rat adenopituitary cells equivalent to that of wild type hGRF(1-29)NH_2 (Table 11).

The obviousness rejections appear to rely, at least in part, on the assertion that the teaching of a binding affinity to the receptor in rat adenopituitary cells would provide a basis for the determination of the analogue [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 as a likely candidate for use in a pharmaceutical composition. Applicant respectfully disagrees.

The presently claimed species (namely, "compound 8" in Gaudreau) is referred to in the present application as "compound 5," (see, e.g., Table 1, # 5 of the present application). Table 11 of Gaudreau discloses various *in vitro* properties of GHRH analogues 1-14. Specifically, Table 11 discloses the IC_{50} values and the relative affinities of each of the GHRH analogues for binding sites present on rat anterior pituitary cells (i.e., the relative affinity of a human GHRH analogue for the corresponding rat GHRH cell surface receptor). These are the only "biological" data that describe any properties of the specific GHRH species at issue.

The MPEP teaches that the "superiority of a property shared with the prior art is evidence of nonobviousness." Specifically, the MPEP states:

> Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut prima facie obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a prima facie case of obviousness." No set number of examples of superiority is required. In re Chupp,

816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut prima facie obviousness even though there was no evidence that the compound was effective against all bacteria).
(MPEP, 716.02 (II)

Applicant has found, unexpectedly, that the binding affinity of the claimed GHRH analogue to the receptor in rat adenopituitary cells is not indicative of the binding affinity for the human GHRH receptor. Applicant notes that the difference between the binding affinity in the rat adenopituitary cells and the human GHRH receptor (hGHRH-R) in baby hamster kidney (BHK) cells transfected with hGHRH-R was discovered during the course of Applicant's subsequent investigation. Applicant's specification states:

[0061] Initial selection of a candidate from the original 14 polysubstituted GHRH analogues described in the U.S. Pat. No. 5,854,216 was based upon *in vitro* data on receptor affinity in 2-month old male Sprague Dawley rat anterior pituitary preparations. The new invention is based on the affinity of selected GHRH analogues for the human GHRH receptor (hGHRH-R) in baby hamster kidney (BHK) cells transfected with hGHRH-R, and on resistance to proteolysis in rat serum, human plasma or human serum. More precisely, the preferred drug candidates were selected, as compared to hGHRH(1-29)-NH_2, for: i--their increased relative binding affinity to hGHRH(1-44)-NH_2 binding sites in rat anterior pituitary *in vitro* as well as to hGHRH-R in BHK-expressing cells *in vitro*; and ii--their relative resistance to proteolysis in vitro.

[0062] As can be noted from Table 1 below, the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor. As will be noted, from this point forward, GHRH analogues as presented in Table 1 will be referred to as GHRH analogues # 1 to 5. (*Emphasis added*)

Applicant's discovery that "the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor" is unexpected and goes against the accepted protocol at the time of the invention. Applicant has herewith submitted a Declaration from Dr. Pierrette Gaudreau (the "Gaudreau Declaration") attesting to the unexpected results of the claimed GHRH analogue.

Dr. Gaudreau has studied various aspects of growth hormone releasing hormone for over twenty years. (See Gaudreau Declaration, paragraph 1). Dr. Gaudreau is also the sole inventor for U.S. Patent No. 5,584,216 and the above-referenced application. Dr. Gaudreau has stated in the declaration that the result that the claimed GHRH analogue that is the lead compound for human clinical trials was unexpected and represents a new discovery that could not have been predicted from the prior work of other researchers and her own patent, U.S. Patent No. 5,584,216 (See Gaudreau Declaration, paragraph 27),

In the field of research for GHRH analogues, it is well accepted that an *in vitro* rat pituitary cell assay is used as a screen to select the most active GHRH analogues for further testing. (See Gaudreau Declaration, paragraph 3). In support of this assertion, Dr. Gaudreau cites numerous papers that show that an *in vitro* rat pituitary cell assay was considered a standard test for testing of GHRH analogues prior to undergoing *in vivo* testing. (See Gaudreau Declaration, paragraphs 3-14). In the papers cited compounds showing an enhanced relative potency and binding affinity compared to a standard during *in vitro* testing using a rat pituitary cell assay were selected for *in vivo* testing. (See Gaudreau Declaration, paragraphs 3-14). In the papers cited, none of the compounds having a relative *in vitro* potency, in the rat pituitary cell assay, that was less than or equal to that of the standard were selected for *in vivo* testing. (See Gaudreau Declaration, paragraphs 3-14)

Given the numerous publications that attest to the correlation between rat pituitary receptor and human receptor activity, Dr. Gaudreau expected that the analogues that exhibited the highest binding affinity to the rat pituitary receptor would also exhibit equally high binding affinity to the human receptor. (See Gaudreau Declaration, paragraph 17). If this expectation were otherwise, the numerous scientists from the listed papers would not have tested their GHRH analogues an *in vitro* rat pituitary cell assay prior to performing *in vivo* and human clinical trials.

After the work performed in conjunction with her earlier patent, U.S. Patent No. 5,584,216, Dr. Gaudreau's research shifted to the discover hGHRH analogues that could have therapeutic utility in humans. Dr, Gaudreau tested various GHRH analogues, prepared during her earlier research on markers for growth hormone-releasing hormone receptors, as reported in U.S Patent No. 5,584,216, for their binding affinity to the human GHRH receptor ("hGHRH-R") in baby hamster kidney cells and the resistance to proteolysis in rat serum, human plasma and human serum. Following the precedent set by numerous other researchers, Dr, Gaudreau focused her attention of compounds that exhibited a higher binding affinity compared to natural hGHRH during *in vitro* testing using a rat pituitary cell assay. Dr. Gaudreau, in a break from precedent, also tested a compound that exhibited a nearly equal binding affinity compared to natural hGHRH during *in vitro* testing using a rat pituitary cell assay. (See Gaudreau Declaration, paragraph 20).

Dr. Gaudreau surprisingly found that [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 binds to the human GHRH receptor of baby hamster kidney cells ("hGHRH-R") with a **>900X** affinity than it binds to the rat GHRH receptor. This result was unexpected and surprising. Dr. Gaudreau notes that other analogues (e.g., analogues #1 and #3, in Applicant's application) follow the expected pattern seen during *in vitro* testing using a rat pituitary cell assay. Specifically, analogue #1 shows a higher binding to hGHRH-R than analogue #3, which is the same pattern seen in the rat model (See Gaudreau Declaration, paragraphs 18 and 21).

Unexpectedly, analogue #5 exhibits the strongest binding affinity for the hGHRH-R model. Given that the first two analogues followed the binding affinity of the rat model, as would be expected based on the numerous publications, the result that analogue 5 exhibited a binding affinity to hGHRH-R that greatly surpassed the binding affinity of the other analogues was a surprising result. (See Gaudreau Declaration, paragraph 22)

In order to select compounds for use in humans, it is important that the compounds not only exhibited enhanced activity, but also are resistant to degradation by the body, in order for the compounds to be able to produce their therapeutic effect. Thus, even if a compound were to exhibit a strong binding affinity for hGHRH-R, if the compound does not exhibit a significant resistance to *in vivo* proteolysis, such a compound would be a poor candidate for use in the treatment of humans. The determination of an ideal candidate for use in human trials is based on a combination of the binding affinity to hGHRH-R and the resistance to proteolysis in human plasma. This combination is known as the "*in vitro* potency index." The *in vitro* potency index is determined by from multiplying (i)-the relative binding affinity of GHRH analogues compared with the native hGHRH (1-29)NH_2, in BHK cells expressing the hGHRH receptor; with (ii)-the relative resistance to *in vitro* proteolysis of compounds in comparison with hGHRH (1-29)NH_2 after preferably 60 or 180 minute-incubations in human plasma or human serum.

The *in vitro* potency index of Applicant's compound D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 is the highest of the analogues tested. (See Applicant's specification, paragraph [0090]). The simultaneous assaying of GHRH analogues, *in vitro* for binding to human GHRH receptor and for their stability in human plasma, lead Dr. Gaudreau to the unexpected selection of analogue 5, [D-Ala^2, D-Tyr^{20}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)NH_2 as the lead candidate for formulation in pharmaceutical compositions and use in human clinical trials.

The superior binding of [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 to human GHRH receptor is not taught or even suggested by any of the cited references. To the contrary, Dr. Gaudreau's patent, U.S. Patent No. 5,584,216, which teaches the binding of the [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 analogue to the rat GHRH receptor, would lead one of ordinary skill in the art to believe that the claimed [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}]hGHRH(1-29)-NH_2 analogue would not bind to human GHRH receptor any better than the wild type hGHRH(1-29)-NH_2. This unexpected result renders the claims unobvious in view of case law and the guidance provided by the above-cited section of the MPEP.

In light of the above, Applicant respectfully submits that claims 48 and 92 are unobvious and patentable over the teachings of Gaudreau, and respectfully requests the withdrawal of the 35 USC §103 rejections.

C. The Claims Are Not Obvious Over The Cited Art Pursuant To 35 U.S.C. § 103(a)

The Examiner has rejected claims 81-91, 93, and 95 as being unpatentable over Gaudreau in further view of U.S. Patent No. 5,137,872 to Seely et al. For at least the same reasons cited above, Applicant submits that claims 81-91, 93, and 95 are allowable over the cited art.

D. Double Patenting Rejection

The Examiner rejected claims 48, 81-91, 93, and 95 under the judicially created doctrine of obviousness-type double patenting over co-pending application no. 12/171,447.

Applicant respectfully disagrees with the double patenting rejection. To expedite prosecution, however, Applicant has submitted a terminal disclaimer for the cited co-pending application.

E. Summary

Based on the above, Applicant submits that all claims are now in condition for allowance. Favorable reconsideration is respectfully requested.

Applicant respectfully requests a three-month extension of time to respond to the Office Action dated May 13, 2009. A fee authorization form is enclosed for the extension of time fee. If any further extension of time is required, Applicant hereby requests the appropriate extension of time. If any fees are inadvertently omitted or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Meyertons, Hood, Kivlin, Kowert & Goetzel, P.C. Deposit Account Number 50-1505/6165-09602/EBM

Respectfully submitted,

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